Cl 1 cont'd

18. (New) The method of claim 8, wherein the retroviral infection is HIV.

REMARKS

Claims 1-16 are pending in this application. Claims 1, 3, 9 and 10 have been cancelled. Claim 2 has been amended to incorporate the variable definitions of Claims 1 and 3. Claims 4, 6, and 11-14 have been amended to correct dependencies. Support for new claims 17 and 18, which define that the retroviral infection is HIV, can be found in the Specification on page 1, line 20, page 2, line 25 and Table 2 (page 321).

No new matter has been added.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1-16 as being obvious over Klaveness et al. (WO 91/06554) in view of Goodman et al. (USPN 5,441,942). The Examiner contends that Klaveness et al. disclose a method for treatment and prophylaxis of retrovirus infections comprising administering compositions of fluorinated nucleosides and pharmaceutically acceptable salts thereof. The Examiner further contends that the references teach that the prior art compounds used in the method may be formulated in a conventional manner by admixture of one or more compounds with excipients and/or carriers. Lastly, the Examiner contends that Klaveness et al. teach that suitable dosages of the prior art compositions lie in the range of 0.1 to 100 mg per kilogram of bodyweight per 24-hour period. The Examiner acknowledges that Klaveness et al. does not specifically disclose a method for treatment and prophylaxis of retrovirus infections using compositions comprising guanosine.

The Examiner also contends that Goodman et al. disclose methods of enhancing an immune response in human and animal cells comprising administering a guanosine composition to a mammal.

The Examiner reasons that since the chemical core of the compounds used in the methods of the instant invention and those of the prior art substantially overlap, as well as the dosage amounts and formulations of the compounds, it would have been obvious for one of ordinary skill in the art to administer to an individual in need thereof a compound comprising a fluorinated nucleoside compound comprising guanosine. The Examiner suggests that one would have been motivated to treat HBV or HIV infections by administering fluorinated nucleosides comprising guanosine since the Klaveness et al. compounds are known to treat retroviruses and the Goodman et al. patent teaches that certain guanosine nucleosides enhance an immune response in human and animal cells. Applicants respectfully traverse.

Applicants first point out that the heart of the instant invention is the use of a novel prodrug approach for ribonucleoside analogues employing an aliphatic amino acid as a prodrug moiety which is now believed to allow transport of the compounds across the gut wall through the active amino acid transport route employed by the non-ribonucleoside herpes agent valaciclovir. The compounds of the invention, however, include a branched alkyl-ester spacer, unlike valaciclovir, that provides an enhanced plasma release of the parent compound. Since the reaction releasing active valaciclovir from the prodrug occurs in the liver and the patients being treated have impaired liver function due to disease (HBV) or co-administered therapy (e.g. ritonavir treatment for HIV), the enhanced plasma release of the active compound increases treatment effectiveness.

Applicants note that Klaveness et al. is a broad patent publication that uses fluorinated nucleosides in a large number of prodrug approaches. Here, the prodrug is applied to the base or the 5' position of the sugar. When the 5' position of the sugar is used, the prodrug moiety

comprises $R_1(O)nCO(OCR_2R_3)$ m-group, which is either esterified (m=0) or alkylated to the 5' position.

The Klaveness et al. alkylated prodrugs are significantly different from the dual esters of the instant invention. First, the nature of the terminal moiety (R_1) does not resemble that of the present invention. Second, the Klaveness esters (i.e. m=0) define R_1 as "optionally substituted alkyl or aryl". The substituent is defined on page 5, line 4, and include "aryl groups preferably having 6-10 carbon atoms (as in arylkyl groupings), alkoxy, hydroxy, acyloxy, amino, acylamino, and carboxy groups)." As a consequence, the Klaveness esters do not extend to, or suggest the further esterification of a hydroxylated alkyl with an aliphatic amino acid.

The Goodman patent fails to fill this void. Goodman describes substituted guanosine nucleosides where the base is disubstituted and the sugar is unsaturated. The 5' position of the sugar is optionally acylated with C_1-C_8 where the acyl group includes such radicals as -C(=O)H, -C(=O)C_1-C_7 alkyl, -C(=O) cyclohexyl, -C(=O) phenyl, and -C(=O) benzyl (see text beginning at column 6, line 14). In contrast, the compounds of the instant invention comprise an unsubstituted guanine base, a highly electronegative 3' fluorine group on the sugar and a 5' hydroxyl that is first esterified with a hydroxylated alkyl ester, which is subsequently esterified with an aliphatic amino acid. Especially in view of the gross differences in structure, Applicants respectfully submit that the simple Goodman esters would not lead the skilled artisan to use the double esters claimed for treatment of HBV and HIV infections.

As a consequence, Applicants respectfully submit that neither Klaveness nor Goodman, individually or in combination, lead to the claimed method of treatment with the particular prodrug confirmation noted in the instant claims.

Applicants also respectfully call the Examiner's attention to the fact that this application is a divisional application of U.S. Patent No. 6,458,772 containing composition of matter claims for the compounds cited in the instant method of treatment claims.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Applicants confirm that the subject matter of the instant invention was commonly owned at the time of the invention.

Conclusion

In view of the above remarks, all the claims remaining in the case as amended are submitted to define non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is requested to contact Leonard R. Svensson (Reg. No. 30,330) in Costa Mesa, California at the (714) 708-8555 to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicant hereby petition for an extension of two (2) months to September 23, 2003 for the period in which to file a response to the Office Action dated April 23, 2003.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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